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The Potential Effect of Using the Cockcroft-Gault Method on Tenofovir-Associated Renal Impairment Reports and on Clinical Decisions Regarding Tenofovir Use in Individual Patients: Implications for the Future

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Abstract

Introduction: In Namibia, the Cockcroft-Gault (C-G) method is recommended for monitoring renal function in HIV patients receiving Tenofovir Disoproxil Fumarate (TDF)-containing Combination Antiretroviral Therapy (cART). However, there are concerns with the potential over-reporting of TDF-associated renal impairment.

Methods: Retrospective study comparing the renal function of patients receiving 2nd line cART with either C-G or Chronic Kidney Disease-Epidemiology (CKD-EPI) methods.

Results: 71 patients were included. The majority (62%) received TDF-containing 1st line ART. All received 2nd-line cART containing TDF/Lamivudine (3TC)/Zidovudine (AZT) and LPV/r. Before switching to 2nd-line cART, 40.8% and 8.5% had abnormal eGFR according to C-G and CKD-EPI methods respectively. During 2nd-line cART, 47.9% and 7% of patients had abnormal eGFR by C-G and CKD-EPI methods, respectively, and 4.1% and 2.8% respectively experienced a decline in eGFR. There was a significant lack of agreement between the two methods.

Conclusion: The C-G method has the potential to report more cases of TDF-associated renal impairment. Consequently, national guidelines in Namibia and other pertinent countries should be reviewed if this is the recommended method for monitoring renal function.

Keywords: Tenofovir; Renal function; eGFR; Cockcroft-Gault; Chronic kidney disease; Epidemiology; Namibia

Background

Antiretroviral (ARV) medicines typically undergo fast-track approval due to the recognised need to improve the quality-of-life and prolong the lives of people infected with the Human Immuno-Deficiency Virus (HIV) [1,2]. Sub-Saharan Africa, being the most affected region of the world with the HIV pandemic, has gained tangible benefits from the use of combination antiretroviral therapy (cART) [3-5]. Despite these tangible benefits, ARV medicines are associated with adverse drug reactions, the impact, incidence, and prevalence of which is not completely measured at the time these medicines are approved for clinical use especially if patients have greater co-morbidities than those enrolled into Phase III trials [6]. Nevertheless, the establishment of pharmacovigilance centres like the Therapeutics Information and Pharmacovigilance Centre (TIPC) in Namibia exposes the safety concerns pertaining to these ARV medicines. This is important in Africa given the appreciable genetic differences between patients in Africa and the western countries where many studies are currently undertaken [7,8].

Earlier in 2016, we published a paper on the 'effect of changing from first-to second-line cART on renal function' [9] studying the effects at a leading health facility in Namibia, from which all patients who were receiving second-line cART (n=71) were included in this study. We used the Cockcroft-Gault (C-G) formula to estimate CrCl [10], because at the time of the study the C-G method was the recommended method in Namibia for assessing renal function in all patients receiving Tenofovir Disoproxil Fumarate (TDF)-containing cART in Namibia [9,11]. TDF is a pro-drug for Tenofovir (TFV) the active ingredient [9], which is known to cause renal impairment by, but not limited to, interfering with the proximal tubular function [12,13]. As such, in Namibia, any TDF dosage adjustments or withdrawals were generally prompted by the estimated CrCl via the C-G formula.

In regards to the monitoring of renal function, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method, which approximates to the Gold-Standard, is known to be better than the C-G method [14]. However as mentioned, the C-G method is the one currently recommended for monitoring renal function in Namibia

[9,11]. However, we do not know the extent to which the C-G method could affect the number of reports of TDF-associated renal impairment. Furthermore, we do not know the effect of the result of renal function assessed by the C-G method can have on subsequent clinical decisions such as a reduction in the dose of TDF or withdrawal of TDF.

Awareness of the superiority of the CKD-EPI method over the C-G method [14] prompted us to use the patients in our earlier study to firstly assess the relationship between the C-G and the CKD-EPI eGFR results. Secondly, ascertain the extent of any differences between the C-G and CKD-EPI methods in the proportion of patients considered to have experienced renal impairment. Lastly, we set out to discover if there was a difference between the C-G and CKD-EPI eGFR results in the number and/or proportion of potential clinical decisions on TDF's dose or TDF's withdrawal.

As a result, guide the authorities in Namibia on whether to continue with recommending the C-G method or change to the CKD-EPI method. This may also have implications for other African resource limited countries if the C-G formula is also being recommended for monitoring renal function in patients who are infected with the HIV and are receiving a cART regimen containing TDF.

Objectives

The first objective of this study was to assess if there was agreement between the eGFR results computed by the C-G and CKD-EPI methods in our study population. The second objective was to identify eGFR results by either the C-G and CKD-EPI methods that met the definition of decline in renal function as per the criteria used in this study, which was also previously used by Kalemeera et al. [9]. These would qualify to be reported as TDF-associated renal impairment to the pharmacovigilance centre. The third objective was to compare the C-G and CKD-EPI methods in the proportions of patients requiring dosage reduction or withdrawal of TDF.

Methods

This was retrospective study assessing the potential effects that the C-G method may have on ADR reports and clinical decisions pertaining to TDF, and comparing these with the CKD-EPI method. This was based on patients receiving second-line cART in out-patients at the Katutura Intermediate Hospital [9]. In the previous study, the C-G method was used to calculate CrCl, which in this study was converted to eGFR using the patients' body surface area (The C-G equation that was used is documented in Box 1).

Dichotomous Grouping of renal function

Any eGFR below 90 ml/min/1.73 m was categorised as abnormal. eGFR was calculated using the C-G and CKD-EPI formulae. For C-G the formula was: [(140–Age) X Weight]/SeCr (X0.85 for females), while for CKD-EPI the general formula was:C X $[(SeCr/0.7)^{e}]$ X $[(0.993)^{Age}]$, where C varied according to ethnicity, and e varied according to the SeCr measurements and sex.

Further categorisation of renal function

The eGFR was further categorised into stages I to IV, where stage I was ≥ 90; stage II was 60–<90; stage III was 30–<60; and stage IV was <30, ml/min/1.73 m^2.

Declined renal function

Renal function was considered to have declined if the last eGFR during second-line cART was ≥ 25% less than the eGFR computed during first-line cART. In addition, when the SeCr was noted to have increased by ≥ 25%, during second-line cART, renal function was considered to have declined.

Improved renal function

Renal function was considered to have improved if the last eGFR during second-line cART was ≥ 25% more than the eGFR during first-line cART. When the SeCr was noted to have decreased by ≥ 25%, during second-line cART, the renal function was considered to have improved, even though the change in eGFR was <25%

Box 1: Definitions of renal function.

We also computed another set of eGFR values using the CKD-EPI method (The CKD-EPI equations that were used are documented in Box 1). The computations of eGFR were based on the last recorded SeCr measurements before patients were switched to second-line cART and the last SeCr measurements during second-line cART. We used the criteria documented in Table 1 to place the patients in the requisite category of renal function. We used the criteria documented in Box 1 to determine if the patient had experienced a decline or improvement in renal function.

To assess the relationship between eGFR values computed by C-G and CKD-EPI methods, we used Cohen's Kappa; Pearson correlation; linear-regression coefficients; and Bland-Altman plots. We used Odds Ratios, Pearson Chi-Square test, Fisher's Exact Test, and Binomial Distribution to assess the difference between the eGFR values computed by C-G and CKD-EPI methods on the potential numbers of reports of TDF-associated renal impairment adverse reactions. Lastly, to assess the potential effect of the eGFR computed by the C-G method on TDF's dose or withdrawal in comparison with the eGFR computed by the CKD-EPI method, we used Odds Ratio. We set the confidence level at 95%, and statistical significance at a p-value <0.05.

Test type	SeCr (mg/dL)	Equations for estimating renal function
Cockcroft-Gault		[(140–Age) X Weight]/SeCr
CKD-EPI(Black female)	≤ 0.7	$166 \times [(SeCr/0.7)^{-0.329}] \times [(0.993)^{Age}]$
	>0.7	$166 \times [(SeCr/0.7)^{-1.209}] \times [(0.993)^{Age}]$
CKD-EPI (Black male)	≤ 0.9	$163 \times [(SeCr/0.7)^{-0.411}] \times [(0.993)^{Age}]$
	>0.9	$163 \times [(SeCr/0.7)^{-1.209}] \times [(0.993)^{Age}]$
CKD-EPI (mixed race - females)	≤ 0.7	$144 \times [(SeCr/0.7)^{-1.209}] \times [(0.993)^{Age}]$
	>0.7	$144 \times [(SeCr/0.7)^{-1.209}] \times [(0.993)^{Age}]$

Table 1: Formulas for evaluating renal function.

Results

Patient characteristics

A total of 71 patients were included in this study. Of these 57.7% (n=41) were female. Table 2 contains details of the mean weight and age before and during second-line cART. 62% (n=44) of the patients received TDF/lamivudine (3TC) and EFV or NVP, and one patient received TDF/FTC/EFV. All patients were receiving a second-line regimen that consisted of TDF/Lamivudine (3TC)/Zidovudine (AZT) and LPV/r. Upon evidence of treatment failure, patients were switched to second-line cART. At the time of data collection, these patients had spent an average of 5.2 ± 2.7 years on first-line cART, and an average of 1.8 ± 0.5 years on second-line cART (Table 2).

	Result
Demographics	
Number of Patients (%)	71 (100)
Average weight, Kg (before 2nd line cART)	62.4 ± 12
Average weight, Kg (during 2nd line ART, at data collection)	64 ± 12
Average Age before switch (years)	42 ± 6.8
Average age at data collection (years)	44 ± 7.1
ART Data	
First-line ART statistics	
No. of patients, received AZT-based first line cART	16 (22.5%)
No. of patients, received D4T-based first line cART	11 (15.5%)
No of patients, received TDF-based first line cART	44 (62.0%)
Second-line ART statistics	
Number receiving TDF/3TC/AZT and LPV/r	71 (100%)
Reasons for switching to second-line ART	
Immunological failure	69 (97.2%)
Virological failure	35 (49.3%)
Clinical failure	3 (4.2%)
Period on ART regimen	
Mean (SD) period (years) spent on first-line cART	5.2 ± 2.7
Mean (SD) period (years) spent on second-line cART	1.8 ± 0.5
SD: Standard Deviation.	

Table 2: Patient Characteristics.

Renal function before second-line therapy

Before switching to second-line ART, the C-G and CKD-EPI methods showed that 40.8% (n=29) and 8.5% of the patients respectively had abnormal renal function (Table 3). During second line cART, the C-G method indicated that more patients (n=10, 14.1%) experienced a decline in renal function, than shown by the CKD-EPI method (n=2, 2.8%). Similarly, the number of patients who experienced an increase in eGFR according to the C-G method (n=6) was slightly lower than those who experienced the same according to the CKD-EPI method (n=8). Moreover, the eGFR calculations during second-line cART yielded similar results to those we observed to have occurred during first-line cART (Table 3).

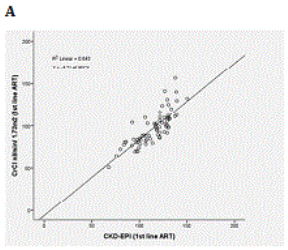
Methods		CKD-EPI: Number (%) of patients per stage					
		During first-line cART			During second-line cART		
		Stage I	Stage II	StageIII	Stage I	Stage II	StageIII
C-G: Number (%) of patients per stage	Stage I	42 (59.2)	-	-	37† (52.1)	-	-
	Stage II	23 (32.4)	5 (7.0)	-	28# (39.5)	2#ß (2.8)	-
	Stage III	-	1 (1.4)	-	2# (2.8)	1#ß (1.4)	1#ß (1.4)
Total		65 (91.6)	6 (8.4)	-	67 (94.4)	3 (4.2)	1 (1.4)

†Includes 6 cases of improved eGFR; #Includes 10 cases of declines in eGFR; ‡Includes 5 new cases of improved eGFR; and ßIncludes one further decline, and 3 new cases of decline in eGFR

Table 3: Number (Percentage) of patients in different stages of renal function as categorised by using the C-G- or the CKD-EPI formulae, before second-line cART.

Assessment of agreement between C-G and CKD-EPI findings

Based on Cohen's kappa, the results show a lack of agreement between C-G and CKD-EPI eGFR computations during first-line cART (kappa=0.224, p=0.003) and during second-line cART (kappa=0.110, p=0.042) (Table 3). Pearson correlation analysis showed that the eGFR for the two methods had a strong relationship (r=0.803; p=0.000) during first-line cART, and there were similar findings during second-line cART (r=0.749; p=0.000), (Figure 1: Panel A and Panel B).



CKD-EPI (C-G) reults during 1st line cART

Stages of renal function	Black females	Black males	Mixed race
Stage I	33 (22)	28 (18)	4 (2)
Stage II	3 (14)	2 (11)	1 (3)
Stage III	-	- (1)	-

CKD-EPI (C-G) reults during 2nd line cART

Stages of renal function	Black females	Black males	Mixed race
Stage I	35 (26)	27 (6)	5 (5)
Stage II	1 (10)	3 (20)	-
Stage III	-	- (4)	-

NB: The distribution of numbers of patients to renal function stages based on the C-G results are in brackets.

Figure 1: Correlation scatter plot for C-G and CKD-EPI measurements of renal function.

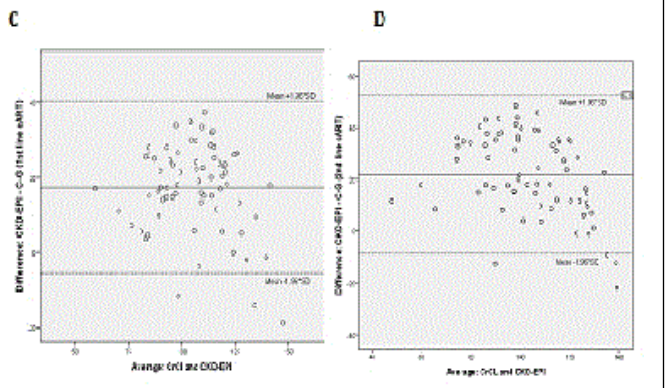


Figure 2: The Bland-Altman Plots comparing the C-G and CKD-EPI methods on measuring renal function.

The correlation scatter plots (Figure 1) show that the eGFR measured by C-G and CKD-EPI correlated strongly. However, the Bland-Altman plots based on the mean bias (standard deviation) during first-line cART: 17.4 (11.4), and during second-line cART: 21.9 (15.6), exposed the absence of agreement between the two tests (Figure 2: Panel C and Panel D). Linear regression analysis confirmed the lack of agreement between the two methods: beta-coefficient of -0.191 (p=0.001), and -0.336 (p=0.001).

Difference between C-G and CKD-EPI

Potential numbers of TDF-associated renal impairment reports

We computed the difference in eGFR between the last measurement during first-line cART and the last measurement during second-line cART, for both C-G and CKD-EPI. We reviewed the magnitude of the difference in eGFR and determined which result met the criteria for decline in renal function. Our findings were that the chance of identifying TDF-associated ADRs with C-G was five times as much as using the CKD-EPI methodology. This finding was significant with the Odds Ratio (Cl 95%; OR=5 (1.06–23.6); p-value=0.04), and also with other tests (Table 4).

	C-G (Number of reports)	CKD-EPI (Number of report)	Odds Ratio (Confidence Interval)	P-Values			
				Odds Ratio	Pearson Chi-Square	Fisher's Exact Test	Binomial Distribution
Assessment of Potential ADRs	10	2	5.0 (1.06–23.6)	0.04	.001	0.027	0.002
Assessment of Potential changes in TDF's dose/ withdrawl	1	0	3.0 (0.12–74.9)	0.5	-	-	-

Table 4: Numbers and analyses of TDF associated renal impairment and TDF dose reduction/withdrawal.

Potential numbers of TDF dose reductions or withdrawals

We assessed each patient's record of eGFR computed by CG and CKD-EPI to determine if the computed eGFR had the potential to recommend a dosage reduction in TDF or its withdrawal. We found that the chance of reducing TDF's dose or withdrawing TDF when C-G is used was three times that of the CKD-EPI methodology (Cl 95%; OR=3.0 (0.12–74.9); p-value=0.05). Since the CKD-EPI results had no patient with an eGFR requiring TDF's dosage reduction, the p-value was only computable for the Odds Ratio (Table 4).

Discussion

Michel et al. and Willems et al. compared the eGFR computed by C-G, CKD-EPI, and Modification of Diet in Renal Disease (MDRD) with the gold-standard. They found that the CKD-EPI and MDRD methods out-performed the C-G method. The C-G method was associated with lower eGFR computations. The authors also found that the CKD-EPI eGFR closely approximated the gold-standard [15,16]. In their study, Matsushita et al. found that CKD-EPI, which out-performs MDRD, led to the reclassification of many patients from lower to higher renal function categories [17]. Since our study was retrospective, and the gold standard is generally not used in clinical practice in Namibia, and because CKD-EPI out-performs MDRD, which out-performs the C-G method [17,18], we compared the C-G based estimations of GFR with those computed by the CKD-EPI method. Since the superiority of CKD-EPI over C-G is an established fact, we did not implement this study to affirm or disprove the CKD-EPI's superiority. However, we set out to highlight the potential impact the lesser method, is the C-G method, may have on the number of reports of TDF-associated renal

impairment in Namibia, and its potential to affect clinical decisions such as TDF's dose reduction or its withdrawal in patients purportedly experiencing renal impairment.

As expected, the C-G method yielded lesser eGFR values than the CKD-EPI method. According to Pearson Correlation analysis, the eGFR results computed by C-G and CKD-EPI had a strong positive correlation. However, according to the Bland-Altman plots (Figure 2) and linear regression analyses, the eGFR results of C-G and CKD-EPI were not close to agreeing. Since the CKD-EPI based method is reflective of the true renal function of the patient, the related eGFR results showed that only a few patients experienced a decline in renal function, contrary to the C-G based estimations, which suggested more patients were experiencing renal impairment. Our findings are similar to Botev et al. study in which the C-G method wrongfully categorised 60% of the study patients into lower renal function categories [19].

Our findings show that the C-G method has implications on TDF's safety because this method yielded a greater proportion of patients with lower stages of renal function before and after switching (Table 3). Furthermore, the C-G method detected more events of decline in renal function (14.0%, n=10) than the CKD-EPI method (2.8%, n=2). Interestingly, our findings indicate that the C-G method has not had implications on TDF's use to any extent different from the CKD-EPI method. This is based on the fact that the majority of patients who were declared to have experienced a decline in renal function *via* the C-G method had an eGFR that was above 50 ml/min, below which dosage adjustments are required [20]. Furthermore, if we assume that eGFR had stabilised at the estimated levels, the C-G based method ceases to pose any challenges of wrongfully categorising patients into lower renal function stages. However, the latter could not be confirmed. In regards to TDF's withdrawal or dosage-interval adjustments due to low eGFR computations, our results show no significant difference between CKD-EPI and C-G (OR=3; p=0.05). However, since the C-G method underestimates eGFR, a significant proportion of patients are likely to miss-out on its use. (NB: The Namibia cART guidelines recommend that before initiating TDF-based first-line cART, the CrCl should be calculated. They also state that initiation of TDF-containing cART should be avoided in cART naïve patients with CrCls below 60 ml/min). Despite the absence of significance in regards to switching or dose reduction in the study patients, there remains a concern that the use of the C-G method may place patients experiencing actual declines of their renal function in categories of lower renal function status, as observed by Botev et al. [19]. Pharmacovigilance centres need to be aware of this fact especially in countries where the C-G method is still used for assessing renal function.

Through the passive reports received by the Therapeutics Information and Pharmacovigilance Centre (TIPC) in Namibia, some work by TIPC has been published [21-23]. Amongst these adverse reaction reports, are reports of renal impairment associated with TDF [21], which were based on reduced CrCl computed by the C-G method. Since the C-G method is likely to raise false alarms of renal impairment, it is likely that some of the reports of TDF-associated renal impairment were not reflective of the actual renal function of the patient. These findings may also be true for other African countries. Consequently, the use of C-G method to assess renal function in patients receiving TDF-containing cART is likely to wrongfully increase the number of reports of TDF-associated renal impairment. Subsequently, the health system's concern for cardiovascular disease in these patients may be escalated. Additionally, the low eGFR computed by the C-G method can influence clinical decisions such as prolongation of TDF's dosage intervals. As a result, subjecting the patients to sub-optimal concentrations of TDF (and 3TC) thereby creating an environment for the emergence of resistance against cART regimens. Lastly, the low eGFR computed by the C-G method can result in TDF's withdrawal.

The addition of the Urine-Dipstick to CrCl as strategy to detect TDF-associated renal impairment is a recent development in cART guidelines [24,25]. The use of the urine dipstick in this regard is based on the fact that the normal nephron would reabsorb all the filtered glucose except in hyperglycaemic patients, who at the detection of glycosuria have plasma glucose levels above the normal threshold for glucose reabsorption: 180 mg/dl [26]. Consequently, the cART guidelines rest on the understanding of the pathophysiology of TDF-associated proximal tubulopathy, during which the reabsorption of glucose is likely interrupted resulting in glycosuria in euglycaemic patients [13,27]. The addition of the urine dipstick is promising to partly or fully negate the possible mis-categorisation of renal impairment by the C-G method in patients receiving TDF-containing cART. This is because the low eGFR in the presence of proximal tubulopathy likely co-occurs with glycosuria and albuminuria. However, we have not found any literature to date that discusses the co-variance of eGFR and urine-glucose or urine-proteins in patients receiving TDF-containing cART. In addition, the sensitivity of the urine dipstick in this patient category needs to be evaluated. This should be the subject of future research. In any event, there are concerns with the C-G method in Namibia and other countries [28,29].

Limitations

The major limitation to our study is that there was no gold standard to compare the C-G- and CKD-EPI-eGFR computations with. It may be that C-G-based assessments identified actual renal impairment cases. We are also aware that we only assessed 71 patients. This is because we built on a previous study conducted in Namibia to address current concerns with the C-G method. However, in view of the findings, we believe our study results are valid, providing guidance to key stakeholder groups in Namibia and throughout Africa. We will be following this up in future studies.

Conclusion

The C-G method is likely to increase the number of reports of renal impairment compared with the CKD-EPI method. The increased incidence in renal impairment reports is of concern to the pharmacovigilance centre, whose critical role is to safe-guard the population against drug related adverse reactions. The disproportionate increase in TDF-associated renal impairment can instigate policy changes in its use. Our study has also shown that the wrong eGFR computations by the C-G method may not influence clinical decisions at the individual patient level, at least not within 2.6 years of second-line cART. It is apparent that within 2.6 years of second line cART, the C-G method did not lead to any clinical decision pertaining to TDF's use such as prolongation of TDF's dosage interval in patients with normal renal function and the withdrawal of TDF from the cART regimen from such patients. The repercussions of such decisions would include the emergence of resistance, new infections with a resistant virus, the replacement of TDF with zidovudine-a less safe ARV medicine than TDF, and lastly increased expenditure on

second-line cART. However, these were not observed. The results of the Urine Dipstick may prove to be beneficial in terms of confirmatory renal function tests. However, the evidence of this is currently lacking. Since TDF-associated nephropathy can be progressive, it is advisable that better methods of renal function assessment than the C-G method, such as the CKD-EPI method, should be considered alongside the use of urine-dipsticks, as this may prevent administration of low doses of TDF instigated by falsely low GFR estimates computed by the C-G method. These are implications for the future in Namibia.

Key Message

The strong positive correlation between eGFR values by C-G and CKD-EPI methods does not necessarily mean that the clinical interpretations of renal function from both tests are the same. It is known that the C-G based method is associated with lower eGFR values than the Gold-Standard, unlike the CKD-EPI method.

In regards to pharmacovigilance, the C-G method of assessment of renal function in patients receiving TDF-containing cART is likely to increase the number of reports of TDF-associated renal impairment, which is not a true reflection of actual renal function. The addition of the urine dipstick may or may not be beneficial in identification of clinical tubulopathy, and thus needs to be evaluated.

When the C-G method is used to assess renal function, the result of reduced eGFR may lead to dose adjustment of TDF, subjecting the patient to sub-therapeutic levels and consequently to the emergence of resistance against TDF.

There is need to utilise better methods to assess renal function in patients receiving TDF-containing cART, such as CKD-EPI as this method more closely reflects the Gold-Standard results.

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